

**Remarks**

Claims 422-429, 431-433, 440-448, 450-452, 459 and 461-479 are presently pending in the subject application. Claims 441-448, 450-452, 459, 461-463, 465 and 473-479 are withdrawn.

Reconsideration and allowance are respectfully requested in view of the above amendments and the following remarks.

Claim 422 has been amended herein in the manner described below.

**Information Disclosure Statement**

The Examiner characterizes the identification of references in Applicants' Reply filed on January 19, 2005 as an information disclosure statement for which an information disclosure statement fee is due under 37 C.F.R. § 1.97(e). Applicants note for the record that Applicants' Reply filed on January 19, 2005 was merely intended to re-identify references for consideration that were previously cited in this application on August 3, 2001 and September 3, 2003. *See* Attachments A and B, copies of Information Disclosure Statements with proof of mailing or facsimile transmission. Each of these prior Information Disclosure Statements included a charge statement.

**Rejoinder of the Process Claims**

The claims elected for examination in the instant application are all directed to a product (*i.e.*, a hybridization assay probe). Therefore, should the Examiner find claim 422, the only independent claim currently being examined, to be allowable, then Applicants respectfully request rejoinder of the process claims, which all depend from claim 422. *See* MPEP § 821.04.

**Rejections Under 35 U.S.C. § 102**

Applicants note with appreciation the Examiner's indication that the rejection of claims 422, 426, 429 and 440 under 35 U.S.C. § 102(b) as being anticipated by Lubini *et al.* (*Current Biology*, 1(1):39-45 (1994)) has been withdrawn.

REPLY

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Claims 422-440 and 464 stand rejected by the Examiner under 35 U.S.C. § 102(e) or 102(a) as being anticipated by Kool *et al.* (U.S. Patent No. 5,514,546). Applicants respectfully traverse this rejection for the reasons that follow.

As noted by the Examiner, the stem-loop oligonucleotides disclosed by Kool form complexes with target nucleic acids which must be at least partially triple-stranded. *See, e.g.*, Kool at column 10, lines 1-5. In the amended claims, however, the recited probe “does not form a triple-stranded structure with the nucleic acid analyte.” This negative limitation is fully supported in the specification at, for example, page 2, lines 15-18, where it is stated that “hybrids usually consist of double-stranded duplexes, although triple-stranded structures are also known.” Although this section refers to probes in a single-stranded form, it was well known in the art at the time the subject application was filed that stem-loop oligonucleotides, when used as probes, preferably lose their secondary structure during or before hybridization to a target nucleic acid. *See* Bagwell (U.S. Patent No. 5,607,834) at column 9, lines 49-53 (“hybridization can be conducted at a temperature either above or below the  $T_m$  of the probe of the present invention as long as single stranded species of both the probe and the target are in existence and are [*sic*] lack secondary structure (hairpins)”; *see also* Diamond *et al.* (U.S. Patent No. 4,766,062) at Figure 3D and column 21, lines 53-68 (both of these patents were previously cited in information disclosure statements filed by Applicants). Furthermore, negative limitations are supported by the Manual of Patent Examining Procedure, where it is stated that “[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.” *See* MPEP § 2173.05(m) at 2100-215 (8<sup>th</sup> ed., Rev. 2, May 2004). Therefore, Applicants submit that Kool fails to disclose each element of the pending claims and, accordingly, withdrawal of this rejection is respectfully requested.

Claims 422-428, 432-433, 440 and 466-472 stand rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Agrawal *et al.* (International Publication No. WO 94/01550). Applicants respectfully traverse this rejection for the reasons that follow.

While Agrawal is cited for disclosing an oligonucleotide having each element of the claimed probes, the Examiner failed to indicate where Agrawal discloses an oligonucleotide having a detectable label, as would be required by the claimed probes. *See* MPEP § 2131.01 at 2100-73 (“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”) (Citation omitted.) The Examiner has also failed to demonstrate a motivation for labeling the oligonucleotides disclosed by Agrawal, as the oligonucleotides of Agrawal are described as therapeutic agents rather than oligonucleotides having a diagnostic use. Accordingly, withdrawal of this rejection is respectfully requested.

**Rejections Under 35 U.S.C. § 103**

Claims 422, 424, 425, 426, 429, 431-433, 440 and 469-472 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Lubini *et al.* (*Current Biology*, 1(1):39-45 (1994)) in view of Tyagi *et al.* (U.S. Patent No. 5,925,517). Applicants respectfully traverse this rejection for the reasons that follow.

The Examiner cites Lubini for teaching a self-complementary RNA-DNA chimera containing some 2'-O-methylated ribonucleotides and DNA residues that are not methylated, where the sequence modified to include the 2'-O-methyl modification is more stable than the unmodified sequence. While acknowledging that Lubini does not teach an oligonucleotide probe comprising a detectable label, the Examiner argues that it would have been obvious to one skilled in the art to add a detectable label, as taught by Tyagi, to the oligonucleotide taught by Lubini. But since Lubini only discloses therapeutic uses of oligonucleotides having 2'-O-methylated ribonucleotides, Applicants submit that there would have been no motivation to modify the oligonucleotides of Lubini to include detectable labels. *See, e.g.*, abstract of Lubini. Moreover, Lubini provides no motivation for modifying Tyagi to include 2'-O-methylated ribonucleotides, since Tyagi cautions that an affinity pair of a unitary probe should interact “sufficiently weakly that the hybridization of the target complement sequence and its target sequence is thermodynamically favored over the interaction of

the affinity pair.” See Tyagi at column 9, lines 45-50. Thus, the proposed modification suggested by the Examiner would render the prior art unsatisfactory for its intended purpose. See MPEP § 2145.X.D. at 2100-161. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 422-429, 431-433, 440, 464 and 466-472 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Yang *et al* (U.S. Patent No. 5,514,551) in view of Agrawal *et al*. (International Publication No. WO 94/01550. Applicants respectfully traverse this rejection for the reasons that follow.

The Examiner cites Yang for teaching a probe having first and second base regions that are capable of hybridizing to each other and forming a hybrid and argues that it would have been obvious to modify these regions to include a 2'-O-methyl substitution, as taught by Agrawal. In fact, the section of Yang cited by the Examiner has nothing to do with self-complementary probes. Instead, this section is concerned with defining the phrase “conservatively modified variants,” and does so by comparing a first nucleotide sequence region of a first nucleic acid with a second nucleotide sequence region of a second, reference nucleic acid. As described in this section of Yang, the conservatively modified variants, which are compared with the second, reference nucleic acid, will form a stable hybrid with the target nucleic acid, which is compared with the first nucleic acid. There is no discussion of oligonucleotides containing these conservatively modified variants self-hybridizing. For this reason, Applicants submit that the Examiner has failed to make out a case of *prima facie* obviousness and, accordingly, withdrawal of this rejection is respectfully requested.

### **Conclusion**

In view of the above amendments and remarks, Applicants submit that the subject application is in condition for allowance and early Notice to that effect is respectfully requested.

REPLY

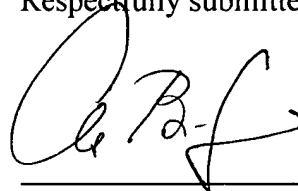
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Please charge the fee due under 37 C.F.R. § 1.17(e), and any other fee which may be due, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

**Certificate of Mailing**

I hereby certify that this correspondence (and any referred to as attached or enclosed) is being deposited with the U.S. Postal Service on the date indicated below with sufficient postage as first class mail addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Respectfully submitted,



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